(1) The application is otherwise approvable.

(2) The application contains the results of studies to determine the compatibility of the large volume parenteral drug product's plastic container with drugs that may be added regularly to the parenteral delivery system.

(h) After February 13, 1979, the Food and Drug Administration shall approve a new drug application for a drug product intended to be added to a parenteral delivery system that includes a large volume parenteral drug product for intravenous use in humans that is packaged in a plastic immediate container if all of the following conditions are met:

(1) The application is otherwise approvable.

(2) The application contains the results of studies to determine the compatibility of the additive drug product with the plastic immediate container of marketed large volume parenteral drug products for intravenous use in humans.

(i) Holders of new drug applications for large volume parenteral drug products that are subject to this section and who must submit supplements under § 314.70(c)(2) of this chapter to provide for the labeling required under paragraph (f) of this section may put the labeling into use without advance approval by the Food and Drug Administration.

(j) This section does not apply to a biological product licensed under the Public Health Service Act of July 1, 1944 (42 U.S.C. 201).

[43 FR 58562, Dec. 15, 1978, as amended at 50 FR 8996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990]

EFFECTIVE DATE NOTE: For a document staying the effectiveness of § 310.509 (g) and (h), see 44 FR 14540, Mar. 13, 1979.

§ 310.510 Use of aerosol drug products containing zirconium.

(a) Aerosol products containing zirconium have been used in over-the-counter drug products as antiperspirants. Based upon the lack of toxicological data adequate to establish a safe level for use and the adverse benefit-to-risk ratio, such aerosol products containing zirconium cannot be considered generally recognized as safe for use in drug products. The benefit from using aerosol drug products containing zirconium is insignificant when compared to the risk. Safer alternative antiperspirant products are available.

(b) Any aerosol drug product containing zirconium is a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application pursuant to section 505 of the act and part 314 of this chapter is required for marketing.

(c) Clinical investigations designed to obtain evidence that any aerosol drug product containing zirconium is safe for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any such drug product introduced in interstate commerce after September 15, 1977 that is not in compliance with this section is subject to regulatory action.

[42 FR 41376, Aug. 16, 1977, as amended at 55 FR 11579, Mar. 29, 1990]

§ 310.513 Chloroform, use as an ingredient (active or inactive) in drug products.

(a) Chloroform has been used as an ingredient in drug products, such as cough preparations, liniments, and toothpastes. Although considered safe for many years, recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats.

(b) Any drug product containing chloroform as an ingredient is a new drug within the meaning of section 201(p) of the act and misbranded and is subject to regulatory action under sections 301, 502, and 505 of the act. Any drug product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

(c) Any holder of an approved new drug application for a drug product containing chloroform as an ingredient shall submit to the Food and Drug Administration on or before July 29, 1976 a supplemental application providing for a revised formulation removing chloroform as an ingredient.

(1) The supplemental application shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) The date that the composition of the drug product will be changed.

(iii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iv) Data available to establish the stability of the revised formulation and, if the data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, a commitment from the applicant:

(*a*) To test the stability of marketed batches at reasonable intervals;

(*b*) To submit the data as they become available; and

(*c*) To recall from the market any batch found to fall outside the approved specifications for the drug.

(v) Copies of the label and all other labeling to be used for the drug product (a total of 12 copies if in final printed form, 4 copies if in draft form).

(2) If such drug product now contains more than one percent chloroform, the revised formulation containing no chloroform shall not be marketed before the receipt of written notice of approval of the supplemental application by the Food and Drug Administration.

(3) If such drug product now contains one percent or less chloroform, the revised formulation containing no chloroform may be marketed, subject to the conditions of §314.70(c) of this chapter, after submission of the supplemental application but prior to the receipt of written notice of its approval by the Food and Drug Administration.

(d) Any sponsor of a ''Investigational New Drug Application'' (IND) for a drug product containing chloroform as an ingredient shall amend the IND on or before July 29, 1976 to revise the formulation removing chloroform as an ingredient.

(e) The Commissioner will initiate action to withdraw approval of an application or terminate an IND in accordance with the applicable provisions of section 505 of the act and parts 312 and 314 of this chapter upon failure of a holder of an approved new drug application or sponsor of an IND to comply with the provisions of paragraph (c) or (d) of this section.

[41 FR 26845, June 29, 1976, as amended at 55 FR 11579, Mar. 29, 1990]

§ 310.515 Patient package inserts for estrogens.

(a) *Requirement for a patient package insert.* FDA concludes that the safe and effective use of drug products containing estrogens requires that patients be fully informed of the benefits and risks involved in the use of these drugs. Accordingly, except as provided in paragraph (e) of this section, each estrogen drug product restricted to prescription distribution, including products containing estrogens in fixed combinations with other drugs, shall be dispensed to patients with a patient package insert containing information concerning the drug's benefits and risks. An estrogen drug product that does not comply with the requirements of this section is misbranded under section 502(a) of the Federal Food, Drug, and Cosmetic Act.

(b) *Distribution requirements.* (1) For estrogen drug products, the manufacturer and distributor shall provide a patient package insert in or with each package of the drug product that the manufacturer or distributor intends to be dispensed to a patient.

(2) In the case of estrogen drug products in bulk packages intended for multiple dispensing, and in the case of injectables in multiple-dose vials, a sufficient number of patient labeling pieces shall be included in or with each package to assure that one piece can be included with each package or dose dispensed or administered to every patient. Each bulk package shall be labeled with instructions to the dispensor to include one patient labeling piece with each package dispensed